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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,565	06/20/2005	Anne-Marie Fernandez	DECL100.001APC	8816
20995 7590 03/10/2008 KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER HEARD, THOMAS SWEENEY	
			ART UNIT 1654	PAPER NUMBER
			NOTIFICATION DATE 03/10/2008	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/522,565	Applicant(s) FERNANDEZ ET AL.	
	Examiner THOMAS S. HEARD	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 and 26-28 is/are pending in the application.
- 4a) Of the above claim(s) 2, 5-9, 13, 14, 16--24 and 26-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 4 and 10-12 is/are rejected.
- 7) ☒ Claim(s) 15 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/12/2007 01/19/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election with traverse of Group I, Claims 1-15, in the reply filed on 10/25/2007 is acknowledged. The traversal is on the ground(s) that:

"As the Examiner will recognize, the practice of the claimed method is not limited to a single compound. R1, R2, R3, R4, R5, R6, R7, R8, R9, and R1 may be substituted with alternate substituents as set forth in the claims and one skilled in the art would reasonably expect the claimed method to proceed as described. It would be unduly limiting for Applicants to be limited to a single species as one skilled in the art could easily avoid infringement of the claim by substitution with alternative substituents which are described by Applicants. Reconsideration of the species restriction is respectfully requested."

This is not found persuasive because an election of species does not limit the Applicants to a single compound. Election of species is for initial search purposes, and if the elected species is found free of the prior art, other species will be search until either prior art found, or the generic is found to be free of the prior art. The requirement is still deemed proper and is therefore made FINAL.

Applicants have elected the compound of Formula Ic where R¹ is a peptide and R² is H. Applicants elected compound has been found free of the prior art. Currently, Claims 1-24 and 26-28 are pending. Claims 16-24 and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 1-15 are hereby examined on the merits. Applicant's elected species is free of the prior art. The Examiner has moved onto the next species and prior art has been applied to Claims 1, 3, 4, and 10-12. Claims 2, 5-9, 13, and 14 are withdrawn as being not being readable upon the claims of the art disclosed species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 1 the term “suitable” is not understood. It is not clear what the claimed material is suitable for. Correction is required.

In Claim 1 the term suitable linker is claimed in line 5 of the text and suitable linker arm in the last line of the claim. It is unclear if these are the same or different linkers. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.' *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ('[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'). Thus, an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations, no that which makes it obvious,' and by using 'such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.' *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when

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accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In *re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, the claims are drawn to a method of synthesis of compounds of Formula (I).

(1) Level of skill and knowledge in the art:

The level of skill to practice the art of the instantly claimed invention is high with regard to chemical synthesis, purification, and chemical characterization post synthesis.

(2) Partial structure: (3) Physical and/or chemical properties: and (4) Functional characteristics:

Compounds of Formula (I) which include doxorubicin, daunorubicin, carminomycin and idarubicin. The doxorubicin, daunorubicin, carminomycin, and idarubicin are cancer compounds which are fused to peptides that aid in cellular transport.

(5) Method of making the claimed invention:

Solution chemistries and solid phase or solution phase peptide synthesis.

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim 1 is a broad generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of linker or linker arm. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. "MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. While having written description for a single linker found on page 20 of the specification, that of sodium maleimidobutyrates in the reaction scheme, there is insufficient description of what constitutes a linker or linker arm that would allow one of skill in the art to practice the invention as claimed. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the

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invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

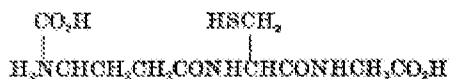
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, and 10-12 rejected under 35 U.S.C. 102(b) as being anticipated by Priebe, et al. "Doxorubicin- and Daunorubicin-Glutathione Conjugates, but not Unconjugated Drugs, Competitively Inhibit Leukotriene C4 Transport Mediated by MRP/GS-H Pump," Biochemical and Biophysical Research Communications, Vol. 247, pp. 859-863, 1998 (Applicant's IDS) and Nicolet, "The Structure of Glutathione," Science, (1930), Vol. LXXI, No. 1849, pages 589-590 for the structure of glutathione.

The instant invention is drawn to a method of making a peptide conjugate of Doxorubicine and other compounds of Doxorubicine that are represented by Formula (I), see Materials and Methods and Synthesis of GS-Dox and –Dau conjugates. Priebe et al discloses the reaction of Doxorubicin and Daunorubicin with Glutathione to form the conjugate of Formula (I). The Final product is formed from conjugating glutathione

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readable on Formula (III) of Claim 1, which contains a free thiol, and R¹ is a NH-Peptide, and R² is a CO-Peptide. The Doxorubicin R⁸ is H, R³ is OCH₃, R⁹ is H, R⁵ is H. R⁶ is OH, R⁴ is H. The Doxorubicin of Formula (II) was brominated at position R⁷ to made the halogenated Doxorubicin of Formula (IIa) where R¹⁰ is Br. The conjugation steps and the Bromination of R7 is readable upon Claims 1, 3, and 4. Given that the compounds are Doxorubicin, and Daunorubicin, and the peptide is three amino acids, the art reads on Claims 10-12. Therefore, the invention, as claimed is anticipated by the prior art.

Claim Objections

Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

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Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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